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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,168	07/14/2006	Kensuke Egashira	GRT/423-74	1356

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,168	EGASHIRA, KENSUKE	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments to the claims filed December 8, 2008 have been received and entered. Claims 1-8, 10, 12-19 have been canceled, while claim 9 has been amended. Applicants have also added claim 20-21. Currently, claims 9, 11, 20 and 21 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II (claims 9-10) in the reply filed on May 14, 2008 was acknowledged. As stated in previous office action, the claimed special technical feature did not contribute over prior art. Therefore, restriction between product and process of using product was found proper. The requirement was deemed proper for the reasons discussed in the previous office action and was therefore made FINAL.

Claims 9, 11, 20 and 21 are under currently under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application 2004-077581, filed in Japan on March 18, 2004. Receipt is acknowledged of certified papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11 remain rejected under 35 U.S.C. 112, first paragraph, as not enabled for the full scope of the invention. The rejection set forth on page 3, of the previous office action dated 9/9/2008 is maintained for the claims 9 and 11 for the reasons of record. Newly added claims 20 and 21 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a method of reducing vascular restenosis following thickened endocardial membrane angioplasty in a subject, comprising administering directly to a injured blood vessel of said subject, a polynucleotide comprising SEQ ID 1 encoding a fibronectin-derived collagen binding domain (FNCBD) and an N-terminal deleted monocyte chemoattractant proteim1 (MCP-1) polypeptide operably linked to a promoter, wherein vascular restenosis at the is reduced in said blood vessel,

(ii) a method of reducing stenosis of an artery in a subject comprising (a) placing an indwelling stent comprising a surface layer which contains an expression vector comprising a polynucleotide comprising SEQ ID 1 encoding a fibronectin-derived collagen binding domain (FNCBD) and an N-terminal deleted monocyte chemoattractant proteim1 (MCP-1) polypeptide operably linked to a promoter, in the artery where the gene elutes from the stent, wherein stenosis of the artery where the stent indwells is inhibited, does not reasonably enable treating restenosis by eluting gene by placing stent at any blood vessel other than one affected and delivering SEQ ID NO: 1 not operably linked to any promoter .

Applicants' arguments filed December 8, 2008 have been fully considered and are persuasive in part. Applicants' amendments to the claims limiting to a method of treating restenosis following thickened endocardial membrane angioplasty obviate the basis of rejection pertaining to treating plurality of vascular disorder caused by post percutaneous transluminal coronary angioplasty (PTCA) or percutaneous transluminal angioplasty (PTA). However, it is noted that claims 9 and 11 as amended still read on placing the gene eluting stent in any blood vessel of

the subject to treat restenosis following thickened endocardial membrane angioplasty. It is emphasized that specification is not enabling for administering gene eluting stent containing a nucleic acid encoding the fusion polypeptides in any blood vessels of a subject to treat restenosis or stenosis other then affected artery for the reasons set forth in previous office action dated 9/9/2008 (see page 8, para. 2). Therefore, this aspect of enablement rejection is maintained for the reasons of record.

Applicants have added new claims 20-21 that are directed to a method of reducing stenosis of an artery in a subject comprising (a) placing an indwelling stent comprising a surface layer which contains the nucleic acid encoding fusion polypeptide of the invention. As stated in previous office action, the state of the prior art with regard to transfer of genes, using a stents, is effectively summarized by the reference of Duverger et al. (U.S. Patent Publication No.: 20030100889, filed Jul. 3, 2002) and Takahashi et al (Gene Ther. 2003; 10(17):1471-8) that showed vectors encoding marker genes could be utilized to deliver genes to the arterial vascular tissue in rabbit and porcine models of restenosis, together with various stents (Duverger et al. paragraphs (0029-0030), (0034-0035) and Example 1 and 2 and abstract of Takahashi). Duverger et al. further describe the inclusion of genes of interest that may be utilized in their gene transfer technique (paragraph 49, page 4). The breadth of the claims embrace delivering nucleic acid into any blood vessel for gene therapy, the prior art effectively addresses the limitations, drawbacks and unpredictability of vectors in transducing cell resulting in therapeutic effect. For example, Thomas et al. (Nature Rev.Genet. 4: 346-358; 2003, art of record) describe the failure of gene delivery after clinical trial failed to show efficacy. Thomas et al States "The stumbling block seemed to be the vehicles that were used to deliver the therapeutic genes to the target tissue; early recombinant viral vectors were inefficient, failed to persist in host cells and transgene expression was typically short lived (column 1, p. 346). It should therefore be noted that expression of any

gene of interest encoded by a simple nucleic acid not operably linked to a regulatory sequence would not be expressed and therefore would not be enabling to treat relapsed stenosis or stenosis. This is supported by Thomas et al. who further state: "the route of vector administration might affect the degree to which cells are transduced; route of administration has a profound effect on the development of T-cell responses to transgenes that are expressed from certain viral vectors (column 2, p. 353, last two paragraphs). In the instant case, the claims as recited do not require the nucleic acid molecule is part of an expression vector operably linked to any regulatory sequences, such as any promoter that permits the expression of nucleic acid molecule in cells of blood vessel. Further, the literature at the time of filing does not provide guidance on how to get RNA polymerase to efficiently prime to a DNA strand that lacks a promoter for sustained period of time for treating vascular restenosis. It is noted that Huang et al (The Journal of Gene Medicine, 2003, 5 900-908) describe the poor transgene expression after naked plasmid injection in skeletal muscle of heart. It is emphasized that Huang et al show inefficient expression from a CMV based plasmid (abstract) because of possible silencing of the promoter in quiescent skeletal and cardiac myocytes (see page 906, col. 2, last para.). Given the unpredictability of gene transfer and variable gene expression, it is apparent that a delivery of polynucleotide encoding hybrid polypeptide not operably linked to any regulatory sequence would not provide expression of transgene that would be required for reducing stenosis. The specification fails to provide guidance with respect to placing stent in any blood vessels in the subject to treat restenosis of a specific blood vessel. In view of the lack of teachings or guidance provided by the specification with regard to treatment of restenosis by placing stent in a blood vessels to treat the vascular restenosis condition in another vessel, and the lack of teachings or guidance provided by the specification with regard to the amount and time necessary for delivery of the hybrid gene without regulatory control sequence subject and for the specific reasons

cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention commensurate with full scope of the claims.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 11 stand rejected under 35 U.S.C. 103(a) and newly added claims 20-21 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Palasis et al (WO/2001/074413, dated 10/11/2001, IDS), Egashira (Hypertension. 2003 Mar;41(3 Pt 2):834-41. Epub 2002 Dec 30, IDS), Ishikawa et al (WO/2002/14505, dated 02/21/2002, relying on 2004/0053368 for English translation, IDS, hereafter 1) and Ishikawa et al (hereafter 2, WO/2000/049159, dated 8/24/2000).

Applicants' arguments filed December 8, 2008, have been fully considered but are not persuasive.

Applicants argue that the working examples of Applicant's specification demonstrate that his stent, which provides a gene encoding the hybrid polypeptide, does reduce stenosis. Applicants assert that the results are unexpected and there is also no evidence cited in his Action that establishes a reasonable expectation of success to use this stent to reduce vascular restenosis.

In response, it is noted that instant specification was indicated as enabling for a method of reducing restenosis following thickened endocardial membrane angioplasty in a subject by placing the stent containing SEQ ID NO: 1 directly into

the affected vessel. The non enabling embodiments included a method of administering stents in any blood vessel not affected by stenosis or restenosis to treat the vascular condition or a method comprising placing any gene eluting stent for the treatment of plurality of vascular disorder caused after percutaneous transluminal coronary angioplasty (PTCA) or percutaneous transluminal angioplasty (PTA) (see specification para. 23). In fact, art teaches gene transfer using a stent, was commonly known in prior art (supra). It is noted that claims recite only one method step comprising placing a stent comprising a surface layer which contains a nucleic acid set forth in SEQ ID 1 encoding a hybrid polypeptide in the artery where the gene elutes from the stent. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). MPEP2111.04 [R-3] states "[C]laim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. In the instant case, wherein clause in the method claim simply expresses the intended result of a process step positively recited.

Deleted: s

With respect to applicants' argument that the working examples of Applicant's specification provides an unexpected reduction of stenosis/restenosis by a gene encoding the hybrid polypeptide (see page 6 of the argument), it is noted Egashira et al teach 7ND MCP-1 gene transfer suppresses monocyte infiltration/activation after arterial injury and markedly inhibits experimental restenosis in animals after balloon injury or stent placement. Furthermore, 7ND MCP-1 gene transfer not only attenuated the development of early atherosclerotic lesions but also limited progression of preexisting atherosclerotic lesions and

changed the lesion composition into a more stable phenotype in hyper-cholesterolemic mice (abstract). Furthermore, effects of 7ND MCP-1 gene transfer on in-stent neointimal hyperplasia are also disclosed by Egashira et al that provides a quantitative comparison of mean percent area stenosis within stent in the empty plasmid-transfected and 7ND-transfected rabbits (see figure 6). Thus, contrary to applicants' assertion of unexpected results, prior art clearly teaches that gene transfer of N-terminal deleted MCP-1 shows significant reduction in restenosis as well as stenosis caused by atherosclerotic lesions. It is emphasized that nucleic acid encoding FNCBD-MCP-1 would have only provided a prolonged, controlled slow release of the physiologically active polypeptide (7ND-MCP-1) as disclosed by Ishikawa (1) and (2). Furthermore, it is emphasized that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). With respect to applicants' submission that the results described in the specification are unexpected, it is emphasized that the arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that how known effect of 7ND in reducing stenosis and restenosis would be unexpected when delivered by stent as set forth in argument upon placing at the affected artery. Given that method of gene transfer by using stent was known as described by Palasis, it would have been obvious for one of ordinary skill in the art to modify the known method of Paslasis to include gene encoding FNCBD-7ND in gene eluting stents to transfer 7ND at the site of injury in blood vessel to reduce restenosis. One of ordinary skill in the art would be motivated to transfer 7ND via gene eluting stent since it was recognized that inflammatory responses to arterial injury causes continuous recruitment and activation of monocytes mainly through activation of the monocyte chemoattractant protein-1 (MCP-1) pathway that results in restenosis

and blockage of MCP-1 by 7ND gene transfer would suppress monocyte infiltration/activation thereby reducing the stenosis.

With respect to applicants' argument of SEQ ID NO: 1 and the specific site of fusing the FNCBD and N-terminal deleted MCP-1 domains in the hybrid polypeptide, it is noted that the SEQ ID NO: 1 is a nucleic acid comprising the sequence of FNCBD that is fused with a N-terminal deleted MCP-1 domain. In the instant case, Ishikawa et al teaches the nucleic acid sequence of FNCBD that has 100% homology with residue 1-1023 of SEQ IDNO: 1, and also teach specific protease recognition sequence for fusing the FNCBD with another nucleic acid (see para. 71 and 72) such as MCP-1 (see para. 61). Egashira et al reported the sequence of an N-terminal deletion mutant of MCP-1, called 7ND, which lacks the N-terminal amino acids 2 to 8, forms inactive heterodimers with wild-type MCP-1 (see figure 1A). Ishikawa (1) also embraced the potential of fusion of the functional polypeptide with the collagen-binding domain having the amino acid sequence of the polypeptide in human fibronectin wherein functional polypeptide included several angiogenic growth factor and MCP-1 (see para. 59 and 61 of the specification). Thus, it would have been obvious for one of ordinary skill in the art to use nucleic acid encoding hybrid polypeptide for prolonged effect of MCP-1 in the treatment of stenosis/restenosis.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 9, 11 were rejected under 35 U.S.C. 103(a), as being unpatentable over Egashira (Presentation at Japanese Society of Gene Therapy Young Investigator Award July, 2003 as appeared in The Journal of Gene Medicine 2005 Dec;7(12):1588-9), Ishikawa et al (WO/2002/14505, dated 02/21/2002, relying on

2004/0053368 for English translation, IDS, hereafter 1) and Ishikawa et al (hereafter 2, WO/2000/049159, dated 8/24/2000) . Applicants' arguments filed December 8, 2008, have been fully considered and are persuasive. Applicants have amended the base claim to include a SEQ ID NO:1 that is not taught by combination of prior art. It is noted that although Egashira teach a method of treating restenosis by placing 7ND-MCP-1 gene eluting stent, but differed from claimed invention by not disclosing the sequence of 7ND-MCP. Therefore, rejection is hereby withdrawn.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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